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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with phenol. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May 1987. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for Phenol. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA-440/5-80-066. NTIS PB 81-117772.

U.S. EPA. 1987. Health and Environmental Effects Profile for Phenol. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. EPA/600/X-87/121. NTIS PB 89-132112/AS.

U.S. EPA. 1988. Integrated Risk Information System (IRIS). Reference dose (RfD) for oral exposure for phenol. Online. (Verification date 11/16/88). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan).

This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RfD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Only one applicable study was found that addressed the toxicological consequences of orally administered phenol. From this chronic study an RfD_{SO} of 42 mg/day and an RfD_O of 42 mg/day were estimated based on the approach suggested by U.S. EPA (1987). This value is supported by descriptive chronic and subchronic studies. These estimates should be reviewed when adequate chronic data are available.

Inhalation exposure data are more limited. A number of subchronic animal studies were located, but all were inadequate for risk assessment as discussed in the text. An RfD_{SI} and RfD_I were not derived. A CS of 44 was calculated for the effects (death and severe histopathological lesions) observed in guinea pigs exposed by inhalation.

All of these estimates should be reviewed when additional data are available.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
CAS	Chemical Abstract Service
CS	Composite score
DMBA	Dimethyl benzanthracene
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RFD_{SI}	Subchronic inhalation reference dose
RFD_{SO}	Subchronic oral reference dose
RV_d	Dose-rating value
RV_e	Effect-rating value
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of phenol (CAS No. 108-95-2) are summarized below.

Chemical class	monocyclic aromatic alcohol
Molecular weight	94.11
Vapor pressure	0.341 mm Hg at 25°C (Mabey et al., 1981)
Water solubility	9.3×10^4 mg/ℓ at 25°C (Callahan et al., 1979)
Density	1.072 (Dow Chemical Co., 1976)
Log K_{ow}:	1.46 (Hansch and Leo, 1985)
Log K_{oc}:	16.2-91 (U.S. EPA, 1987)
Bioconcentration factor	2 (Kobayashi et al., 1979)
Half-life in Air:	7-15 hours (Atkinson, 1985; NLM, 1987)
Water:	<1-9 days (NLM, 1987)
Soil:	<2-35 days (Baker and Mayfield, 1980; Ehrlich et al., 1982)

Phenol will biodegrade completely in soil in 2-5 days (Baker and Mayfield, 1980; Ehrlich et al., 1982; Delfino and Dube, 1976). Because of its high water solubility and poor adsorption to soil, phenol is expected to be highly mobile in soil; nevertheless, biodegradation is sufficiently rapid so that phenol may biodegrade before reaching groundwater, except in cases of spills or similar situations where high concentrations of phenol may destroy degrading microbial populations (Ehrlich et al., 1982; Delfino and Dube, 1976).

The primary removal process for phenol in water is biodegradation. Degradation will be faster in freshwater systems than in estuarine waters and faster under aerobic conditions than anaerobic conditions. Photooxidation may also be an important removal mechanism in humic waters where the concentration of alkylperoxy radicals is significant (NLM, 1987).

In air, phenol is expected to react with photochemically generated hydroxyl radicals. Because of the lack of data on direct photolysis, the atmospheric half-life reported above is for reaction with hydroxyl radicals only. The relatively high water solubility of phenol suggests that significant amounts of this compound would also be removed from the atmosphere in precipitation (NLM, 1987).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Deichmann and Keplinger (1981) reported that phenol is readily absorbed following oral administration. Humphrey et al. (1980) investigated the disappearance of a 40 mg/kg dose of ^{14}C-phenol from the *in situ* isolated small intestine of Sprague-Dawley rats. Disappearance of radioactivity appeared to follow first order kinetics with a half-time of 5.5±0.5 minutes and a rate constant for intestinal absorption of 0.127±0.003 min^{-1}.

2.2. INHALATION

Piotrowski (1971) exposed human volunteers (seven males, one female) to vapors of phenol through facemasks (6-20 mg/m^3) for 8 hours. By measuring respiratory volume and the concentration of phenol in inspired and expired air, it was estimated that 60-80% of the inhaled dose was retained throughout the period of exposure, regardless of the inspired concentration.

Ohtsuji and Ikeda (1972) found free phenol and conjugated phenol in the urine of workers exposed to 0.0 (7), 0.6 (7), 4.2 (4), 7.8 (8), 8.8 (8), 9.6 (8) and 12.5 mg/m^3 (7 subjects) phenol (estimated from air samples). Levels of total phenols in the urine varied proportionally with the levels of phenol in the atmosphere. The authors compared the amount of phenol inhaled/hour with the amount excreted/hour and concluded that pnenol is readily absorbed by inhalation.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Subchronic and chronic oral toxicity data are summarized in Table 3-1. In an unpublished study conducted by Dow Chemical Co. (1945, 1976) phenol was administered by gavage (vehicle not specified) to rats at 10, 100 and 200 mg/kg/day in 20 daily doses. Slight liver and kidney effects were reported at the highest dose only. Subsequently, a total of 135 doses of 50 and 100 mg/kg/day phenol was administered by gavage to rats 5 days/week over a 6-month period. At the high dose, slight liver and moderate kidney damage was observed; at the low dose, only slight kidney damage was reported. A LOAEL of 50 mg/kg/day (TWA = 35.7 mg/kg/day) was established on the basis of kidney damage (U.S. EPA, 1988).

A 90-day range finding study was conducted by NCI (1980) to determine the concentration of phenol to be used in F344 rats and B6C3F1 mice for a 2-year carcinogenesis bioassay. The compound was administered in drinking water at five concentrations: 0, 100, 300, 1000, 3000 and 10,000 ppm (0, 19, 57, 190, 570 and 1900 mg/kg bw/day) (Table 3-1). Decreased weight gain resulting from rejection of water was reported in both sexes of both species at the highest dose level. No other effects were observed.

Two additional subchronic oral studies were mentioned in U.S. EPA (1987); however, these studies were available only as English abstracts from the foreign literature, details were poorly presented and the quality of the studies was uncertain.

3.1.2. Inhalation. Three subchronic inhalation studies reported by NIOSH (1976) are summarized in Table 3-2.

In the subchronic study by Deichmann et al. (1944), guinea pigs, rats and rabbits exhibited a wide range of sensitivities to 100 mg/m^3 phenol.

TABLE 3-1

Subchronic and Chronic Oral Toxicity of Phenol[a]

Species/Strain	No. of Animals	Dose (mg/kg bw/day)	Route	Length of Exposure	Effects	Reference
Mice/B6C3F1	10M, 10F/ group	0, 19, 57, 190, 570, 1900	oral in drinking water	90 days	No effects noted from 0-3000 ppm in any parameter studied (body weight, appearance, behavior, food and water consumption, histological examination of tissues). At 10,000 ppm decreased water consumption, decreased weight gain (80% less in males, 33% less in females), no histopathological changes	NCI, 1980
	50M, 50F	475	oral in drinking water	103 weeks	Decreased weight gain, decreased water consumption (75% of control)	
	50M, 50F	950	oral in drinking water	103 weeks	Decreased weight gain, decreased water consumption (50-60% of control)	
Rats/F344	10M, 10F/ group	0, 14, 42, 140 420, 1400	oral in drinking water	90 days	No effects noted from 0-3000 ppm in any parameter studied (body weight, appearance, behavior, food and water consumption, histological examination of tissues). At 10,000 ppm decreased water consumption, decreased weight gain (16% less in males, 26% less in females), no histopathological changes	NCI, 1980
	50M, 50F	350	oral in drinking water	103 weeks	Decreased mean body weight gain, decreased water consumption (80% of control)	
	50M, 50F	700	oral in drinking water	103 weeks	Decreased mean weight gain, decreased water consumption (90% of control), chronic kidney inflammation in male ($p \leq 0.00191$) and female ($p \leq 0.00001$, Fisher's Exact Test) rats.	
Rats/NR	NR	0, 112, 168, 224, 280 and 336	oral in drinking water	12 months	Weight gain depressed at two highest dose levels. No other significant differences noted between control and experimental animals.	Deichmann and Oesper, 1940
Rats/NR	NR	200 mg/kg/day	oral (gavage)	20 daily doses	Slight liver and kidney effects	Dow Chemical Co., 1945, 1976
	NR	10 or 100 mg/kg/day	oral (gavage)	20 daily doses	No liver or kidney effects noted	

TABLE 3-1 (cont.)

Species/Strain	No. of Animals	Dose (mg/kg bw/day)	Route	Length of Exposure	Effects	Reference
Rats/NR	NR	100 mg/kg/day 5 days/week	oral (gavage)	6 months	Slight liver changes and slight to moderate kidney damage	Dow Chemical Co., 1945
	NR	50 mg/kg/day 5 days/week	oral (gavage)	6 months	Slight kidney damage	
Rats/NR	NR	14, 70, 140	oral in drinking water	5 generations	No deleterious effect	Heller and Pursell, 1938
	NR	420, 700	oral in drinking water	3 generations	No significant effect	
	NR	980	oral in drinking water	2 generations	Below normal growth in young	
	NR	1120	oral in drinking water	2 generations	Decreased water intake, occasional irritability, impaired mothering behavior, many young died, below normal growth rate	
	NR	1400	oral in drinking water	NR	Offspring died at birth, retarded growth rate	
	NR	1680	oral in drinking water	NR	Retarded growth rate, no reproduction, mature animals died in hot weather	
Rats/CD	20-22F	30 or 60	oral (gavage)	gestational days 6-15	No maternal toxicity or evidence of teratologic effects	NTP, 1983
	20-22F	120	oral (gavage)	gestational days 6-15	Reduced fetal body weight with no signs of maternal toxicity	NTP, 1983

[a]Source: U.S. EPA, 1987

[b]The concentrations correspond to average intakes of 0, 21, 30, 49, 56 and 55 mg/rat/day, respectively, based on actual water consumption data.

NR = Not reported

TABLE 3-2

Subchronic Exposure to Phenol by Inhalation*

Species	No. of Animals	Dose (mg/kg bw/day)	Exposure Period	Effects	Reference
Guinea pigs	12 treated, no controls	9.92-19.84	7 hours/day, 5 days/week for 20 days	Five deaths; weight loss, signs of paralysis; pathological changes included extensive necrosis of the myocardium, acute lobular pneumonia, vascular damage, renal and hepatic damage.	Deichmann et al., 1944
Rabbits	6 treated, no controls	5.48-10.96	7 hours/day, 5 days/week for 88 days	No external signs of toxicity; pathological changes included lobular pneumonia, chronic degeneration of pulmonary blood vessels, liver and kidney damage.	
Rats	15 treated, no controls	6.64-13.27	7 hours/day, 5 days/week for 74 days	No internal or external signs of toxicity	
Rats	50 treated, 50 controls	1.44	8 hours/day, 5 days/week for 90 days	No significant difference between treated animals and controls with respect to kidney function or hematological or urological variables. There was a slight gain in body weight for treated rats and monkeys and increased "endurance" (as indicated in stress test) in mice.	Sandage, 1961
Monkeys	10 treated, 10 controls	1.53	8 hours/day, 5 days/week for 90 days		
Mice	100 treated, 100 controls	2.94	8 hours/day, 5 days/week for 90 days		
Rats	15/treatment group	0, 0.001, 0.009 and 0.409	continuous, 61 days	No effects at 0.01 mg/m³; extensor muscle chronaxy was significantly different from controls at 0.11 mg/m³. Blood cholinesterase activity was slightly increased at 0.11 mg/m³, but no other effects were observed. Animals treated at 5.2 mg/m³ were sluggish, exhibited lower rates of weight gain, had significantly increased blood cholinesterase activity, and had shortened extensor muscle chronaxy and lengthened flexor muscle chronaxy.	Mukhitov, 1964

*Assumed 50% absorption

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This dose corresponds to 9.92, 13.27 and 0.44 mg/kg bw/day phenol for guinea pigs, rats and rabbits, respectively, assuming U.S. EPA (1986) reference values for animal weight and breathing rate. Of 12 treated guinea pigs, 5 died after only 28 days of exposure. The others had weight loss, signs of paralysis and numerous pathological changes. In contrast, rats given the same level of exposure for 74 days had no external or internal signs of toxicity. Pathological changes in the absence of external signs of toxicity were reported for rabbits exposed to phenol at a level of 5.48 mg/kg bw/day.

Rats, mice and monkeys exposed by inhalation to phenol at levels of 1.44, 2.94 and 1.53 mg/kg bw/day respectively, for 8 hours/day, 5 days/week for 90 days had no significant adverse toxic effects when compared with control animals (Sandage, 1961).

In contrast, Mukhitov (1964) observed adverse effects of exposure to phenol in rats at the 0.009 and 0.409 mg/kg bw/day levels of exposure. In this study, however, rats were exposed continuously for 61 days, whereas in the study by Sandage (1961), rats were exposed noncontinuously for 90 days.

3.2. CHRONIC

3.2.1. Oral. Four studies regarding the chronic toxicity resulting from oral exposure to phenol were located in the available literature and were summarized in Table 3-1. In the NCI (1980) bioassay (Section 4.2.1.), a treatment-related increase in the incidence of chronic kidney inflammation was reported in high-dose male and female rats. The incidences in males were 37/50, 37/50 and 48/52 for the control, low and high doses, respectively. The incidences in females were 7/50, 13/50, and 28/50 for the control, low and high doses, respectively. Statistical significance was not reported by the authors, but the Fisher Exact test (U.S. EPA, 1987) revealed highly significant differences for the incidence in high-dose males ($p=0.00191$) and for the incidence in high-dose females ($p=0.00001$).

Heller and Pursell (1938) administered phenol in the drinking water of rats at 0-12,000 ppm (0, 14, 70, 140, 420, 700, 980, 1120, 1400 and 1680 mg/kg bw/day) for 1 year or 2, 3 or 5 generations (see Table 3-1). The lack of pathological examinations or functional tests in this study precludes the use of these data in the calculation of an RfD_0 for human ingestion of phenol.

Deichmann and Oesper (1940) administered six concentrations of phenol in the drinking water of rats for 12 months (see Table 3-1). A decreased weight gain at the two highest dose levels was the only effect reported.

A teratologic study of phenol effect was performed in timed-pregnant CD rats (NTP, 1983). Phenol was administered in distilled water by gavage at 0, 30, 60 and 120 mg/kg/day on gestation days 6-15. Groups of 20-22 females per dose were weighed, observed for signs of toxicity and sacrificed on gestation day 20. No signs of maternal toxicity or any dose-related clinical symptoms were observed. There were no significant differences between treatment groups in the number of implantation sites or in the number of live fetuses per litter. There was a small but significant increase in the number of preimplantation losses between the 30 and 60 mg/kg/day groups and the untreated controls but not for the 120 mg/kg/day group. However, since implantation takes place before the first treatment, which is to gestation day 6, no relationship between phenol treatment and the number of implantation sites could be determined. A detailed teratologic examination, conducted at sacrifice on gestation day 20, revealed a highly significant reduction in fetal body weight in the 120 mg/kg/day group. A NOAEL without maternal toxicity was determined to be 60 mg/kg/day. These data were also described by Jones-Price et al. (1983a,b) and are more fully detailed in Section 3.3.1.

3.2.2. Inhalation. Pertinent data regarding chronic exposure to phenol by inhalation could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. The teratogenicity of phenol was investigated by Jones-Price et al. (1983a,b) in both Sprague-Dawley CD rats and CD-1 mice. Phenol, in distilled water (0, 30, 60 or 120 mg/kg/day), was administered by gavage to timed-pregnant rats (23/group) on gestation days 6-15 (Jones-Price et al., 1983a). The animals were sacrificed on day 20 of gestation. No signs of maternal toxicity were observed. A significant increase in the proportion of litters with resorption sites was observed at the 30 and 60 mg/kg/day doses, ($p<0.05$ and $p<0.01$, respectively), but not at the 120 mg/kg/day level. The number of implantations was significantly increased in the low and medium dose groups, however, and no differences were observed in the percentage of resorptions per litter. The number of live fetuses per litter, sex ratio of the litters, the percentage of affected fetuses per litter and the proportion of litters with dead or malformed fetuses did not differ among treated groups, but average fetal body weight per litter showed a significant dose-related ($p<0.001$) decrease. There was also a significant ($p<0.01$) difference between the controls and the high-dose group. No structural teratogenic effects resulting from administration of phenol were reported.

Phenol (0, 70, 140 and 280 mg/kg/day) was administered by gavage in a concurrent study (Jones-Price et al., 1983b) to timed-pregnant CD-1 mice (31-36/group) on gestation days 6-15. The dams were sacrificed on day 17 of gestation. Weight loss, tremors, ataxia, lethargy and irritability were reported in high-dose dams. Other indications of maternal toxicity included

increased mortality in the high-dose group (11 vs. 0 in other groups), and statistically significant dose-related trends for decreased body weight and gravid uterine weight that were significantly ($p<0.01$) lower in the high-dose group compared with the controls. Numbers of implantation sites per dam, fetal viability or structural abnormalities of fetuses were not significantly different among groups. Dose-related decreases ($p<0.001$ for trend) in mean fetal body weight per litter were reported; a significantly lower ($p<0.001$) body weight was reported in the highest dose group compared with controls. The incidence of cleft palate was 0/308, 1/290, 1/280 and 8/214 for the 0, 70, 140 and 280 mg/kg/day dose groups, respectively; however, the differences were not statistically significant. The fetal effects occurred at doses that also produced maternal toxicity, and were probably secondary to the maternal stress. Reproductive effects in rats associated with ingestion of phenol in rats were reported in the drinking water study by Heller and Pursell (1938) and are summarized in Table 3-1. Growth of offspring was retarded at $\geq$980 mg/kg bw/day; impaired mothering and neonated death occurred at $\geq$1120 mg/kg bw/day; offspring dying at birth occurred at 1400 mg/kg bw/day; and there was no reproduction at 1680 mg/kg bw/day.

3.3.2. Inhalation. Pertinent data regarding the developmental or reproductive toxicity of inhaled phenol were not located in the available literature.

3.4. TOXICANT INTERACTIONS

Pertinent data regarding toxicant interactions between phenol and other compounds were not located in the available literature; however, Challis (1973) reported that phenol and nitrites could react to form p-nitrosophenol under *in vitro* conditions.

4. CARCINOGENICITY

4.1. HUMAN DATA

Data pertaining to the carcinogenicity of phenol in humans were not located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. An NCI (1980) bioassay of phenol was conducted to test F344 rats and B6C3F1 mice for possible carcinogenicity. Phenol was administered in the drinking water to groups of 50 male and 50 female rats and 50 male and 50 female mice at concentrations of 0, 2500 and 5000 ppm for 103 weeks. A dose-related decrease in weight gain was reported in treated animals, which was attributed to decreased water consumption. No other clinical signs were observed. Survival was comparable among control and treated groups. Statistically significant increased incidences of leukemias or lymphomas were reported in low-dose male rats compared with controls. The incidences in high-dose males were also higher but were not significantly different from matched controls. In low-dose male rats, the incidence of interstitial cell tumors of the testis was increased when compared with controls. Low-dose male rats also had a significant incidence of C-cell carcinomas in the thyroid and pheochromocytomas in the adrenals. No increased incidences of tumors were reported in female rats or in female or male mice. Based on the high spontaneous tumor rate observed in matched controls and the lack of a positive effect in the high-dose groups the association between phenol and cancer is not clearly established. NCI (1980) concludes that phenol is not carcinogenic under conditions of this bioassay. It was suggested by the reviewers, however, that phenol be considered for retesting because of the equivocal results obtained in male rats.

4.2.2. Inhalation. Data pertaining to the carcinogenicity of inhaled phenol in animals were not located in the available literature.

4.3. OTHER RELEVANT DATA

Phenol was reported to be mutagenic to Escherichia coli, but only at concentrations of phenol (0.1-0.2%) that caused a reduction in survival (0.5-1.7% survival) (Demerec et al., 1951). In an in vitro experiment, phenol induced mutation in gonads of Drosophila (Hadorn and Niggli, 1946). Dickey et al. (1949) reported that phenol was not mutagenic to Neurospora.

Negative results were reported with and without S-9 in an assay using histidine auxotrophs of Salmonella typhimurium (Pool and Lin, 1982). Haworth et al. (1983) and Florin et al. (1980) reported that phenol did not exhibit mutagenic activity in similar tests using the same strains of S. typhimurium that were used by Pool and Lin (1982). Gocke et al. (1981), however, reported mutagenic activity in one strain of S. typhimurium with S-9, which was evaluated by the above investigators with negative results.

Boutwell and Bosch (1959) investigated the tumor-promoting ability of phenol in skin painting experiments with several strains of mice and using DMBA as an initiator. Phenol appeared to be a weak complete carcinogen in these studies. Phenol apparently initiated and promoted the development of skin papillomas and carcinomas, particularly in a strain of mice selected for sensitivity to DMBA initiation and croton oil promotion. Similar results were obtained by Salaman and Glendenning (1957) in strain "S" mice.

4.4. WEIGHT OF EVIDENCE

IARC has not evaluated the risk to humans associated with oral or inhalation exposure to phenol. Phenol was administered in the drinking water of mice and rats for 2 years at levels of 2500 and 5000 ppm (NCI, 1980).

Statistically significant increased incidences of pheochromocytomas of the adrenal medulla, C-cell carcinoma of the thyroid and leukemias or lymphomas were reported in male rats at 2500 ppm but not at 5000 ppm. No increased tumor incidences were observed in female rats or female and male mice. NCI (1980) concluded that phenol was not carcinogenic under the conditions of the bioassay and it was suggested that phenol be considered for retesting. Applying the U.S. EPA (1986) criteria for overall weight of evidence of carcinogenicity to humans, data are inadequate and the chemical is most appropriately designated a Group D - Not Classified chemical. This is consistent with the analysis by U.S. EPA (1987).

5. REGULATORY STANDARDS AND CRITERIA

Based on subchronic animal studies (Deichmann et al., 1944), the American Conference of Governmental Industrial Hygienists established a TWA-TLV of 5 ppm (19 mg/m³) and a STEL of 10 ppm (38 mg/m³) (ACGIH, 1986a,b). NIOSH (1976) recommended a TWA-TLV for a 10-hour workday, 40-hour week of 20 mg/m³, and a 60 mg/m³ ceiling for a period of exposure not to exceed 15 minutes. The OSHA (1985) occupational permissible exposure limit for phenol is also 5 ppm (19 mg/m³). The Public Health Service drinking water standard for phenols is 1.0 µg/ℓ (U.S. DHEW, 1962).

Based on the subchronic study by Dow Chemical Co. (1976) and using a safety factor of 500, the U.S. EPA (1980a) calculated an interim ADI of 0.1 mg/kg/day or 7.0 mg/man/day for ingestion of phenol. From this interim ADI, and assuming that 2.0 ℓ water/day and 0.0065 kg fish/day (with a bioconcentration factor of 2.0) are consumed by the reference 70 kg man, an interim ADI for drinking water of 3.5 mg/ℓ was calculated. Since an organoleptic threshold (taste) of 0.3 mg/ℓ was reported, however, a criterion level for phenol in water of 0.3 mg/ℓ was established.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}). Based on the rat study by NTP (1983), a NOAEL of 60 mg/kg/day was established (see Section 3.1.1.) for reduced fetal body weight. U.S. EPA (1988) verified a chronic RfD based upon this same study because the exposure was considered to be chronic for the fetus. They chose a composite uncertainty factor (UF) of 100 (10 for intraspecies, 10 for interspecies). Medium confidence is placed in this RfD_{SO}. Analysis of the data regarding the oral toxicity of phenol is expanded in Section 6.2.1.

6.1.2. Inhalation (RfD_{SI}). As discussed in Section 3.1.2., the available subchronic data are not suitable for use in quantitative risk assessment.

U.S. EPA (1987) calculated a CS for the effects (death, severe signs of toxicity and extensive histopathological changes) observed in guinea pigs exposed to atmospheric phenol at 100 mg/m³ 7 hours/day, 5 days/week for a total of 29 exposures (Deichmann et al., 1944). The resulting exposure corresponded to 4.96 mg/kg/day. A chronic human MED of 5.6 mg/day was calculated, which is equivalent to an RV_d of 4.4. An RV_e of 10 was chosen to represent mortality, the most severe effect. A CS of 44, the product of RV_d and RV_e, results in an RQ of 10. The complete derivation of this value is presented in U.S. EPA (1987).

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_O). As discussed in Section 3.2.1. and summarized in Table 3-1, four chronic oral studies were located in the literature. Data from both the Heller and Pursell (1938) and Deichmann and Oesper (1940) studies presented no pathological or functional evaluation and therefore are

unsuitable for use in risk assessment. Based on a verified analysis presented by the U.S. EPA (1987b), the LOAEL of 50 mg/kg/day from the Dow Chemical Co. (1945) study was used as a basis for a chronic oral RfD. Further review indicated that a teratologic study using rats would be preferable because the exposure was considered to be chronic for the fetus. The LOAEL for reduced fetal body weight was determined to be 120 mg/kg/day and the NOAEL was 60 mg/kg/day. Applying an uncertainty factor of 100 results in an RfD_O of 0.6 mg/kg/day or 42 mg/day for a 70 kg man (U.S. EPA, 1988). Confidence in this value was rated medium.

6.2.2. Inhalation (RfD_I). Data pertaining to the chronic toxicity of inhaled phenol were not located in the available literature, and, as discussed in Section 3.1.2., the available subchronic data are not suitable for use in quantitative risk assessment. An RfD_I, therefore, is not calculated.

6.3. CARCINOGENIC POTENCY (q_1*)

The lack of pertinent data regarding the carcinogenicity of phenol precludes the assessment of carcinogenic risk.

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APPENDIX

Summary Table for Phenol

	Species	Experimental Dose/Exposure (mg/kg/day)	Effect	Reference Dose (RfD or RfD_S)	Reference
Inhalation					
RfD_{SI} (formerly AIS)		Not calculated because of lack of data			
RfD_I (formerly AIC)		Not calculated because of lack of data			
Maximum composite score	guinea pig	100 mg/m³ 7 hours/day, 5 days/week for 29 exposures (RV_d = 4.4)	death, severe toxicity and histopathological lesions (RV_e = 10)	44	Deichmann et al., 1944; U.S. EPA, 1987
Oral					
RfD_{SO}	rat	NOAEL = 60 mg/kg/day	reduced fetal body weight	0.6 mg/kg/day (42 mg/day for 70 kg man)	NTP, 1983; U.S. EPA, 1987
RfD_O	rat	NOAEL = 60 mg/kg/day	reduced fetal body weight	0.6 mg/kg/day (42 mg/day for 70 kg man)	NTP, 1983; U.S. EPA, 1987